

WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.**

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

*https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[MA079 trade name][†]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of artesunate and 200 mg of mefloquine (as hydrochloride)

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Blue, round, smooth, biconvex, film-coated tablets.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA079 trade name] is indicated for the treatment of uncomplicated malaria. [MA079 trade name] is active against all *Plasmodium* parasites that cause malaria in humans.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

4.2 Posology and method of administration

Oral use.

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms.

It is preferable that the patient has a positive diagnostic test before administration.

Posology

The recommended daily dose range of artesunate/mefloquine is between 2–10 mg of artesunate and 7–11 mg of mefloquine per kg body weight.

[MA079 trade name] may be used in patients weighing 18 kg or more. For patients in lower weight bands, another formulation should be used to supply the correct dose.

Patients weighing 18 kg or more

[MA079 trade name] is taken once daily for 3 days as indicated in the table below. It is important to ensure that the number of tablets (packs) supplied to the patient is sufficient for a full 3-day treatment course.

Patient body weight	Number of tablets	Dose of active substances supplied
18 to less than 30 kg	1 tablet once daily	100 mg artesunate/200 mg mefloquine once daily
30 kg or more	2 tablets once daily	200 mg artesunate/400 mg mefloquine once daily

If a patient gets malaria within 60 days of treatment with [MA079 trade name], a different artemisinin-based

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

[#] Formerly known as Cipla Limited

combination therapy (ACT) should be used for treatment. Repeating a course of [MA079 trade name] within 60 days is not recommended due to increased risk of neuropsychiatric reactions.

Missed dose and vomiting after a dose

If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.

Patients who vomit within 30 minutes of taking the medicine should repeat the dose.

Special populations

Pregnancy

Treatment with artesunate/mefloquine at standard doses is recommended by WHO to treat uncomplicated falciparum malaria during the second and third trimester of pregnancy. The combination may be considered for use in the first trimester where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available.

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal impairment.

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions. Caution should be exercised when using [MA079 trade name] in patients with impaired liver function. [MA079 trade name] should not be used in patients with severe hepatic impairment.

Elderly

No dosage adjustments are necessary in elderly patients.

Method of administration

The tablets should be swallowed whole preferably after a meal with plenty of liquid.

For patients unable to swallow the tablets, [MA079 trade name] may be crushed and mixed with water. The mixture should be swallowed immediately after preparation.

4.3 Contraindications

[MA079 trade name] is contraindicated in:

- patients with known hypersensitivity to artesunate, mefloquine or related compounds (e.g. quinine, quinidine) or to any of the excipients.
- patients with severe malaria according to WHO definition.
- patients halofantrine
- in patients with a history of blackwater fever, a complication of falciparum malaria with massive intravascular haemolysis causing haemoglobinuria.
- in patients with severe hepatic impairment (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Neuropsychiatric reactions

Mefloquine can cause psychiatric symptoms, including anxiety, paranoia, depression, hallucinations, and psychosis. Some mental health changes, such as trouble sleeping, strange dreams, intense anxiety, depression, agitation, or confusion, could be warning signs of a more serious problem (see section 4.8). There have also been reports of suicide, suicidal thoughts, and self-harm associated with mefloquine use (see section 4.8).

Malaria may return despite the use of an effective antimalarial treatment and a good initial clinical response. This can occur if the patient has a late treatment failure (i.e. after an initial reduction in parasite counts, they increase again due to failure to achieve complete parasite clearance) or if patients who remain in the malaria endemic region become reinfected. If there is a reappearance of clinical symptoms and signs of malaria, the

patient should be immediately evaluated and, if clinically indicated, effective antimalarial treatment should be prescribed. [MA079 trade name] should not be used within two months of a therapeutic dose of mefloquine because of the increased risk of mefloquine-induced neuropsychiatric side effects.

Eye disorders

Any patient presenting with a visual disorder should be referred to a physician as certain conditions (such as retinal disorders or optic neuropathy) may require stopping treatment with mefloquine.

Cardiac toxicity

Patients with underlying cardiac conduction defects or known cardiac arrhythmias: In rare cases, treatment and prophylaxis with mefloquine have been associated with clinically significant adverse events related to cardiac conduction. The risk is QTc prolongation should be considered when co-administering [MA079 trade name] with certain medicines. (see section 4.5)

Seizure disorders

In patients with a history of seizures, [MA079 trade name] may increase the risk of convulsions

Renal impairment

Patients with renal impairment as there is limited data on use in renal impairment

Inhibitors and Inducers of CYP3A4

Patients taking inhibitors and inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentrations (see section 4.5).

Impaired liver function

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions.

Neuropathy

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine.

Mefloquine should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Blood and lymphatic system disorders

Cases of agranulocytosis and aplastic anaemia have been reported during mefloquine therapy (see section 4.8).

Pneumonitis

Pneumonitis of possible allergic etiology has been reported in patients receiving mefloquine (see section 4.8). Patients who develop signs of dyspnoea, dry cough or fever etc. while receiving mefloquine should be advised to contact a doctor to undergo medical evaluation.

Interaction with vaccines

When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunisation cannot be excluded. Vaccinations with oral attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine (see section 4.5).

Hypoglycaemia

The possibility of hypoglycaemia in patients with congenital hyperinsulinaemic hypoglycaemia should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

[MA079 trade name] should not be used in patients taking medicines that are known to prolong the QTc interval (see section 4.3), as effects may be additive and increase the risk of cardiac arrhythmia.

[MA079 trade name] should not be given concurrently with any other antimalarial agent unless there is no other treatment option, due to limited data on safety and efficacy. In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering [MA079 trade name] to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments. See also the table below.

Interactions with particular medicines

Whenever co-prescribing any drug together with [MA079 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with [MA079 trade name] is not exhaustive but is a selection of interactions of potential relevance.

Drugs (grouped by therapeutic area)	Interaction	Recommendation on co-administration
Antimalarials		
Halofantrine	Potential additive/synergistic effects on QT-interval	Co-administration is contraindicated. [MA079 trade name] should not be given until at least 15 weeks month after the last halofantrine dose due to the long elimination half-life of halofantrine.
Quinine	Risk of QTc prolongation associated with concurrent use of quinine and mefloquine	Use with caution and appropriate monitoring.
HIV antiretrovirals		
<i>Nucleoside/nucleotide transcriptase inhibitors</i>		
Abacavir Emtricitabine Lamivudine Tenofovir disoproxil or alafenamide Zidovudine	Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is considered unlikely	No additional measures needed.
<i>Non-nucleoside/nucleotide transcriptase inhibitors</i>		
Efavirenz	Co-administration has not been studied. Mefloquine is metabolized by CYP3A4.	Efavirenz could potentially decrease artesunate and mefloquine exposure which may impair efficacy.
Etravirine	Co-administration has not been studied. Mefloquine is metabolized by CYP3A4.	Etravirine could potentially decrease artesunate and mefloquine exposure which may impair efficacy.
Nevirapine	Co-administration has not been studied. Mefloquine is metabolized by CYP3A4.	Nevirapine could potentially decrease artesunate and mefloquine exposure which may impair efficacy.
Rilpivirine	Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely.	Caution is nonetheless advisable with co-administration since rilpivirine may prolong the QT-interval at higher doses.
Doravirine	Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.	No additional measures needed.

Drugs (grouped by therapeutic area)	Interaction	Recommendation on co-administration
<i>HIV protease inhibitors</i>		
Atazanavir	Coadministration has not been studied but atazanavir may increase plasma levels of artemisinins and mefloquine.	Caution is required since both mefloquine and atazanavir may prolong the QT-interval.
Darunavir	Coadministration has not been studied but darunavir may increase plasma levels of mefloquine.	Use with caution due to the potential increase in mefloquine exposure.
Lopinavir/ritonavir	Lopinavir C_{max} ↓ 23% AUC ↓ 22% artesunate C_{max} ↑ 59% AUC ↑ 52% dihydroartemisinin C_{max} ↓ 37% AUC ↓ 49% mefloquine C_{max} ↓ 13% AUC ↓ 28%	The reduction in drug exposure raises concerns for an increased risk of treatment failure for malaria and HIV. In addition, caution is required since both mefloquine and lopinavir can prolong the QT-interval.
<i>Integrase strand transfer inhibitors (INSTIs)</i>		
Elvitegravir/Cobicistat	Co-administration has not been studied. Elvitegravir/cobicistat may increase concentrations of artemisinins and mefloquine.	Monitor patients for side effects if co-administration is required.
<i>Pharmacokinetic enhancers</i>		
Ritonavir	Co-administration may decrease dihydroartemisinin exposure.	Caution is recommended in co-administration.
Cobicistat	Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and mefloquine by inhibition of CYP3A4.	Monitor patients for side effects if co-administration is required.
Antivirals for hepatitis B/C		
Ombitasvir/paritaprevir/ritonavir	Mefloquine exposure may ↑ Mefloquine is a substrate of CYP3A4.	Co-administration of mefloquine with is not recommended unless the benefit outweighs the risk due to QTc prolongation. If unavoidable, patients should be closely monitored.
Daclatasvir	Co-administration has not been studied. Mefloquine and daclatasvir are substrates and inhibitors of P-glycoprotein and concentrations of both drugs may increase.	Clinical relevance of increases via this mechanism is uncertain.
Antifungals		
Ketoconazole	Mefloquine C_{max} ↑ 64% AUC ↑ 79%	Co-administration is contraindicated due to increased risk of QTc prolongation when ketoconazole is taken with mefloquine.

Drugs (grouped by therapeutic area)	Interaction	Recommendation on co-administration
Antiepileptics		
Carbamazepine Phenytoin	Concomitant use of strong inducers of CYP3A4 such as carbamazepine and phenytoin may decrease dihydroartemisinin exposure, leading to a reduction in, or loss of, efficacy. In addition, concomitant administration of mefloquine and anticonvulsants (e.g. carbamazepine or phenytoin) may reduce seizure control by lowering the plasma levels of anticonvulsant.	Co-administration should be avoided.
Antituberculars		
Rifampicin	Concomitant use of rifampicin may decrease dihydroartemisinin and mefloquine exposure, leading to a reduction in, or loss of, efficacy. Patients taking this drug should be followed up carefully to identify treatment failures.	Co-administration should be avoided.
Anticancers		
Axitinib Vandetanib Imatinib	These agents may increase dihydroartemisinin exposure due to UGT enzyme inhibition, leading to a reduction in, or loss of, efficacy.	Co-administration should be avoided if possible.
Other		
Diclofenac	Diclofenac may increase dihydroartemisinin exposure due to UGT enzyme inhibition, leading to a reduction in, or loss of, efficacy	Co-administration should be avoided if possible.
Tramadol	Co-administration may increase risk of convulsions	Caution recommended in co-administration

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[MA079 trade name] can be used during the second and third trimester of pregnancy.

[MA079 trade name] may be used during the first trimester of pregnancy when the first-line option (artemether-lumefantrine) is not suitable or available.

Breastfeeding

Animal data suggest excretion of [MA079 trade name] into breast milk, but the amounts that enter breast milk and are consumed by breastfeeding infants are expected to be relatively small. In line with WHO guidelines, [MA079 trade name] can be used in breastfeeding women.

Fertility

There is no information on the effects of [MA079 trade name] on fertility in humans.

4.7 Effects on ability to drive and use machines

[MA079 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving [MA079 trade name] should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable effects

Adverse events considered at least possibly related to mefloquine and artesunate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($1/100 - 1/10$), uncommon ($1/1000 - 1/100$), rare ($1/10\,000 - 1/1000$), very rare ($< 1/10\,000$) or not known (frequency cannot be estimated from available data).

Blood and lymphatic systems disorders

	Artesunate	Mefloquine
<i>Very common</i>	Anaemia, post-treatment delayed haemodialysis, mild and transient decrease in reticulocyte count	
<i>Not known</i>	Immune haemolytic anaemia	agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia

Immune system disorders

<i>Not known</i>	anaphylaxis	hypersensitivity from mild cutaneous events to anaphylaxis
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Metabolism and nutrition disorders

<i>Uncommon</i>	amorexia	decreased appetite
<i>Not known</i>		

Psychiatric disorders

<i>Very common</i>		abnormal dreams, insomnia
<i>Common</i>		depression, anxiety
<i>Not known</i>		suicide, attempted suicide, suicidal ideation and self-endangering behavior, bipolar disorder, psychotic disorder including e.g. delusional disorder, depersonalization, mania, and schizophrenia/schizophreniform disorder, paranoia, panic attacks, confusional state, hallucinations, aggression, agitation, restlessness, mood swings, disturbance in attention

Nervous system disorders

<i>Common</i>	dizziness, headache	dizziness, headache
<i>Not known</i>		encephalopathy, cranial nerve paralysis, convulsions, amnesia (sometimes long lasting for more than 3 months), syncope, speech disorder, memory impairment, balance disorder, gait disturbance, peripheral motor neuropathy (including paraesthesia,

		tremor and ataxia), peripheral sensory neuropathy, somnolence
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Eye disorders

<i>Common</i>		visual impairment
<i>Not known</i>		cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment, vision blurred

Ear and labyrinth disorders

<i>Common</i>		vertigo
<i>Not known</i>		vestibular disorders including tinnitus, partial deafness (sometimes prolonged), hearing impaired, hyperacusis

Cardiac disorders

<i>Common</i>	bradycardia	
<i>Not known</i>	QT prolongation	AV block, tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder

Vascular disorders

<i>Common</i>	hypotension, phlebitis	
<i>Uncommon</i>	flushing	
<i>Not known</i>		cardiovascular disorders (hypotension, hypertension, flushing)

Respiratory, thoracic and mediastinal disorders

<i>Common</i>	cough, nasal symptoms	
<i>Not known</i>		pneumonia, pneumonitis of possible allergic etiology, dyspnoea

Gastrointestinal disorders

<i>Common</i>	altered taste, vomiting, diarrhoea, abdominal pain or cramps	nausea, diarrhoea, abdominal pain, vomiting
<i>Uncommon</i>	Nausea, constipation	
<i>Not known</i>		pancreatitis, dyspepsia

Hepatobiliary disorders

<i>Common</i>	transient rises in liver transaminases (AST, ALT), hyperbilirubinaemia, jaundice	
<i>Not known</i>		hepatic failure, hepatitis, jaundice, asymptomatic transient transaminase (ALT, AST, GGT) increased

Skin and subcutaneous tissue disorders

<i>Common</i>		pruritus
<i>Uncommon</i>	Stevens-Johnson syndrome, pruritus, rash, urticaria	
<i>Not known</i>		Stevens-Johnson syndrome, erythema multiforme, rash, erythema, urticaria, alopecia, hyperhidrosis

Musculoskeletal and connective tissue disorders

<i>Common</i>	arthralgia, muscle disorders	
<i>Not known</i>		muscular weakness, muscle spasms, myalgia, arthralgia

General disorders and administration site conditions

<i>Common</i>	fever	
<i>Uncommon</i>	fatigue	
<i>Not known</i>		oedema, chest pain, asthenia, chills, pyrexia, malaise, fatigue

Renal and urinary disorder

<i>Common</i>	Haemoglobinuria, acute renal failure	
<i>Not known</i>		renal failure acute, nephritis, blood creatinine increased

* The frequency of artesunate side effects is based on injectable artesunate

Abnormal dreams/nightmares

Abnormal dreams and insomnia are very common adverse reactions with mefloquine, therefore their significance should be considered in the overall evaluation of patients reporting reactions or changes to their mental state with mefloquine (see warning section 4.4).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Artesunate

Experience of acute overdose with artesunate is limited. A case of overdose has been documented in a 5 year-old child who was inadvertently administered rectal artesunate at a dose of 88 mg/kg/day over 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose. The overdose was associated with pancytopenia, melena, seizures, multi-organ failure and death.

Treatment of overdose should consist of general supportive measures.

Mefloquine

In cases of overdosage with mefloquine, the symptoms mentioned under section 4.8 may be more pronounced.

Patients should be managed by symptomatic and supportive care following mefloquine overdose. There are

no specific antidotes. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disorders. Elimination of mefloquine and its metabolites is limited by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials; Artemisinin and derivatives, combinations, ATC code: P01BF02

Mechanism of action

Artesunate

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, *Artemisia annua* L.), a plant which has been used for centuries in traditional Chinese medicine.

The mechanism of action of the artemisinins likely involves cleavage of the internal endoperoxide bridge through reaction with haeme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calcium adenosine triphosphatase.

The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate and the artemisinins are the most rapid acting of the antimalarials, and they have also been shown to enhance splenic clearance of infected erythrocytes by reducing cytoadherence.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of *P. falciparum*.

Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizonts or merozoites.

Mefloquine

Mefloquine acts on and destroys the asexual intraerythrocytic forms of the human malaria parasites: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. It is effective in the treatment and prophylaxis of malaria. Mefloquine is also effective against malarial parasites resistant to other antimalarials such as chloroquine and other 4-aminoquinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulphonamide combinations.

Clinical efficacy and safety

The efficacy of [MA079 trade name] will depend on the drug sensitivities of the local malaria parasites. Resistance has been evidenced by a decline in cure rates of artesunate plus mefloquine given as separate tablets in Western Cambodia and a slowing of parasite clearance in North-Western Thailand.

An open-label clinical study in 500 patients (adults and children) was conducted in North-Western Thailand. Patients treated with artesunate/mefloquine 100/200mg fixed dose combination experienced a Day 63 PCR-corrected cure rate of 91.9% (95% CI 88.2, 95.6), while those treated with the standard loose tablet regimen of artesunate and mefloquine displayed a Day 63 PCR-corrected cure rate of 89.2% (95% CI 85.0, 93.4; Kaplan-Meier analysis, log-rank test for significance).

In an additional, randomized open-label study in 50 adult patients with acute, *uncomplicated P. falciparum* malaria conducted in Thailand, 22/24 patients (91.7%) patients treated with Artesunate/Mefloquine

100/200mg fixed dose combination had parasitological cure at day 28, compared to 24/24 (100%) patients administered artesunate and mefloquine as separate tablets.

An open-label, single-arm study with Artesunate/Mefloquine 100/200mg fixed dose combination in 77 adult patients with acute, uncomplicated *P. falciparum* malaria conducted in India reported 63-day parasitological cure rates of 100%.

5.2 Pharmacokinetic properties

The absorption characteristics of [MA079 trade name] have been determined after administration of two tablets in healthy volunteers in the fasting state as follows

Pharmacokinetic variable	Arithmetic mean ± standard deviation	
	Artesunate	Mefloquine
Maximum concentration (C _{max})	138 ± 56 ng/mL	716 ± 217 ng/mL
Area under the curve (AUC _{0-∞}), a measure of the extent of absorption	182 ± 144 ng.h/mL	378 ± 124 µg/mL
Time to attain maximum concentration (T _{max})	0.6 ± 0.8 h	24 ± 25 h

The absorption characteristics have also been determined after administration of two tablets once daily for 3 days in patients with *P. falciparum* malaria as follows

Pharmacokinetic variable	Arithmetic mean ± standard deviation	
	Artesunate	Mefloquine
Maximum concentration (C _{max})	249 ± 266 ng/mL	3279 ± 1252 ng/mL
Area under the curve (AUC _{0-∞}), a measure of the extent of absorption	780 ± 675 ng.h/mL	1193 ± 634 µg/mL
Time to attain maximum concentration (T _{max})	0.8 ± 0.7 h	72 ± 19 h

Pharmacokinetics of artesunate and mefloquine

	Artesunate	Mefloquine
General		
	In patients with malaria, single PK parameters may differ from those in healthy subjects.	
Absorption		
Absolute bioavailability	NA*	NA*
Oral bioavailability	After absorption, artesunate is rapidly and extensively metabolised to its main active metabolite dihydroartemisinin.	The bioavailability of tablets compared with the oral solution of mefloquine is over 85%.
Food effect	Exposure increased by 43% with a high fat/high calorie meal	Food significantly increases absorption and increases bioavailability by 40%
Distribution		
Volume of distribution	Artesunate: 15 L/kg	20 L/kg

	Dihydroartemisinin: 1.6-2.6 L/kg	
Plasma protein binding <i>in vitro</i>	Artesunate: 75% Dihydroartemisinin: 47 – 76%	98%
Tissue distribution ¹	Dihydroartemisinin accumulates substantially in <i>P. falciparum</i> -infected erythrocytes	Distributed to blood, urine, CSF, and tissues; concentrated in erythrocytes, with concentrations almost twice as high as plasma concentrations. Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal.
Metabolism		
	Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6.	Extensively metabolised in the liver by CYP3A4.
Active metabolites	Dihydroartemisinin is further metabolised through glucuronidation	NA*
Elimination		
Elimination half life	Artesunate: 3–29 minutes Dihydroartemisinin: About 2 hours	21 days in healthy subjects; 14 days in malaria patients
Mean systemic clearance (Cl/F)	Artesunate: 20 L/kg/h Dihydroartemisinin: 1.4 – 2.7 L/h/kg	0.022 to 0.073 L/h/kg
Pharmacokinetic linearity	NA*	NA*

*Information not available

Special populations

Renal impairment

No specific recommendations available regarding need for dosage adjustment in individuals with renal impairment.

Hepatic impairment

In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma concentrations.

Pregnant women

Clearance of mefloquine may increase in late pregnancy, however, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

5.3 Preclinical safety data

General toxicity

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Similar to artesunate, mefloquine has a higher tolerance compared to therapeutic doses. However, exceeding recommended dosages can lead to toxicity. Studies in rats and dogs administered repeated doses of mefloquine have shown toxicity at levels exceeding the proposed human therapeutic dose. The specific effects vary depending on the species and dose, but some reported findings include central nervous system (CNS) effects, gastrointestinal effects as well as effects on the liver and kidneys. Effects on the heart, blood

cells, and reproductive system have also been reported in some studies with high-dose mefloquine administration in rats and dogs.

Genotoxicity

Artesunate did not show any mutagenic or clastogenic potential in in vitro and in vivo tests (Ames, mouse micronucleus).

Mutagenicity tests indicated that activation of mefloquine hydrochloride produced mutagenic products that mediated base-pair substitution mutation in the *E. coli* WP2 trp (pEB017) tester strains. The *S. typhimurium* his TA97 strains also mediated a weak frameshift mutation but mefloquine mutagenicity potential was most remarkable as a base pair substitutions mutagen. Mefloquine hydrochloride exhibits base-pair substitution mutagenesis and is not strictly genotoxic.

Carcinogenesis

No studies of the carcinogenic potential of artesunate and mefloquine have been conducted.

Reproductive toxicology studies

Oral artesunate caused dose-dependent fetal toxicity in rats, rabbits, and monkeys, resulting in fetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3- and 7-day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12-day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced. A study of artesunate administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were reversible after cessation of treatment.

Mefloquine was teratogenic in mice and rats and embryotoxic in rabbits; however, large clinical experience with mefloquine as prophylactic treatment has not revealed an embryotoxic or teratogenic effect. Data from a limited number of exposed pregnancies indicate no adverse effects of mefloquine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Mefloquine is also secreted into breast milk in small amounts.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect, and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs), and following single oral doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20 and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

In vitro, mefloquine blocks preferentially the slow (I_{Ks}) component of the delayed rectifier potassium (K^+) channel in cardiac muscle and, therefore theoretically has the potential to exacerbate the QTc prolongation produced by other drugs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Croscarmellose sodium,
magnesium stearate and
microcrystalline cellulose.

Film coat: Indigo carmine aluminium lake (FD & C Blue #2),

hypromellose,
macrogol,
polysorbate 80 and
titanium dioxide.

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Primary packing: Aluminium-aluminium blister strip with 3 tablets.

Secondary packing: Carton having one strip of 3 tablets and carton having 2 strips of 3 tablets.

6.6 Special precautions for disposal and other handling

Not applicable

7. SUPPLIER

Cipla Limited
Cipla House,
Peninsula Business Park,
Ganpatrao Kadam Marg,
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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA079

9. DATE OF PREQUALIFICATION

12 September 2012

10. DATE OF REVISION OF THE TEXT

June 2025

References

General reference sources for this SmPC include:

WHO guidelines for malaria, 14 March 2023. Available at:
<https://apps.who.int/iris/rest/bitstreams/1493946/retrieve>

Artesunate Amivas injection European Medicines Agency SmPC
https://www.ema.europa.eu/en/documents/product-information/artesunate-amivas-epar-product-information_en.pdf

Mefloquine 250 mg tablets UK SPC
<https://www.medicines.org.uk/emc/product/13896/smpc#gref>

Section 4.5

University of Liverpool, HIV and Hepatitis Drug Interactions websites. Available at:
<https://www.hiv-druginteractions.org/>
<https://www.hep-druginteractions.org/>

Na-Bangchang K, Tan-Ariya P, Thanavibul A, Riengchainam S, Shrestha SB, Karbwang J. Pharmacokinetic and pharmacodynamic interactions of mefloquine and quinine. *Int J Clin Pharmacol Res.* 1999;19(3):73-82. PMID: 10761536.
<https://pubmed.ncbi.nlm.nih.gov/10761536/>

Section 4.6 and others (information related to use in pregnancy)

Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015) - WHO Malaria Policy Advisory Committee and Secretariat. Available at:
<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-016-1169-x>

Dellicour S, Sevene E, McGready R et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. *PLoS Med* 2017; 14(5): e1002290: <https://doi.org/10.1371/journal.pmed.1002290>

Saito M, McGready R, Tinto H, et al. Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis. *Lancet* 2020 Mefloquine 250 mg tablets. Available at: [https://doi.org/10.1016/S0140-6736\(22\)01881-5](https://doi.org/10.1016/S0140-6736(22)01881-5)

Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, Oo AP, Naing AL, Nyo MY, Myint NZ, Imwong M, Ashley E, Lee SJ, White NJ. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Infect Dis.* 2010 Oct;10(10):673-81. doi: 10.1016/S1473-3099(10)70187-0. Epub 2010 Sep 9. PMID: 20832366; PMCID: PMC2947715.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947715/>

Ashley, E. A., Lwin, K. M., McGready, R., Simon, W. H., Phaiphun, L., Proux, S., ... Nosten, F. (2006). An open label randomized comparison of mefloquine-artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *Tropical Medicine & International Health*, 11(11), 1653-1660. <https://doi.org/10.1111/j.1365-3156.2006.01724.x>

Akerele, J. O., & Obaseiki-Ebor, E. E. (2002). Studies on the Genotoxic and Mutagenic Potentials of Mefloquine. *Tropical Journal of Pharmaceutical Research*, 1(2), 91-98.

file:///C:/Users/fmasekela/Downloads/ajol-file-journals_80_articles_14589_submission_proof_14589-949-27207-1-10-20040213.pdf

All weblinks were last accessed on 22 June 2025.

Detailed information on this medicine is available on the World Health Organization (WHO) website:
<https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>

